Cyclosporine in Anti-Jo1-positive Patients with Corticosteroid-refractory Interstitial Lung Disease

Lorenzo Cavagna, Roberto Caporali, Lul Abdì-Alì, Roberto Dore, Federica Meloni, and Carlomaurizio Montecucco

ABSTRACT. ***Objective.*** To describe the longterm effectiveness and safety of cyclosporine (CYC) in patients with anti-Jo1-positive antisynthetase syndrome with corticosteroid-refractory interstitial lung disease (ILD).

Methods. All patients with anti-Jo1 antisynthetase syndrome referred to our division between June 1991 and February 2010 were retrospectively evaluated for ILD. ILD was assessed using pulmonary function tests (PFT) and/or high-resolution computed tomography (HRCT). Kazerooni score was used to evaluate the HRCT extent of ILD. Prednisone was the first-line treatment in all cases (1 mg/kg/day orally, then tapering). Patients with corticosteroid-refractory or relapsing ILD were then included in this retrospective study. All patients started CYC (3 mg/kg/day) without increasing prednisone dosage. Both PFT and chest HRCT were regularly reassessed during followup.

Results. Over the period of study we evaluated 18 patients with antisynthetase syndrome; 17 had ILD (13 women; median age at ILD onset 57 yrs); all patients failed prednisone within 12 months of ILD onset and subsequently started CYC. The median followup on CYC was 96 months [interquartile range (IQR) 57–120 mo]. Upon starting CYC, median forced vital capacity (FVC) was 60% (IQR 56%–70%), median DLCO 60% (IQR 50%–62.75%), and median Kazerooni score 16 (IQR 7–18). After 1 year of CYC, FVC ($p = 0.0006$), DLCO ($p = 0.0010$), and total Kazerooni score ($p = 0.0002$) improved and prednisone was tapered (median reduced from 25 mg/day to 2.5 mg/day; $p < 0.0001$). The results were substantially maintained including at last available followup. CYC side effects were hypertension (5 patients) and creatinine increase (6 patients). CYC was reduced in 3 cases and withdrawn in 4. Three out of 4 patients who interrupted CYC experienced ILD relapse; 2 patients recommenced low-dose CYC with subsequent ILD control. One patient refused re-treatment and subsequently died.

Conclusion. CYC is effective and substantially safe in patients with anti-Jo1 antisynthetase syndrome with corticosteroid-refractory ILD. CYC withdrawal may be associated with ILD relapse, and low-dose CYC was effective in ILD control. (First Release Feb 15 2013; J Rheumatol 2013;40:484–92; doi:10.3899/jrheum.121026)

Key Indexing Terms:
ANTI-JO1 ANTISYNTHETASE SYNDROME INTERSTITIAL LUNG DISEASE
CORTICOSTEROID-REFRACTORY CYCLOSPORINE

Aminoacyl-tRNA synthetases are a group of cytoplasmic enzymes that catalyze aminoacyl-tRNA synthesis and thus protein synthesis. The antibodies linked to these enzymes are the serological markers of a rare subset of polymyositis/dermatomyositis (PM/DM), characterized by the occurrence of Raynaud phenomenon, peripheral arthritis, typical cutaneous manifestations (e.g., mechanic's hands), and interstitial lung disease (ILD): the antisynthetase syndrome[1]. Among the different antisynthetase antibodies, histidyl-tRNA (anti-Jo1) is the most common target, being found in up to 20% of patients with PM/DM[2,3]. Other antibodies are directed against the aminoacyl-tRNA synthetase for threonine (PL-7), alanine (PL-12), glycine (E3), asparagine (K5), and isoleucine (O)[1]. Pulmonary fibrosis is observed in up to 85% of patients with antisynthetase syndrome, a much higher frequency than in classic PM/DM[1,4]. Therefore, ILD in antisynthetase syndrome is different from that commonly described in PM/DM not only in prevalence, but also due to other peculiarities, as suggested by previous proteomic studies[5]. ILD is the major determinant of morbidity and mortality in antisynthetase syndrome in general[6] and in patients with anti-PL7 and anti-PL12 specificities in particular[7].

From the Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo, Pavia; and IRCCS Foundation S. Maugeri, Castel Goffredo, Italy.

L. Cavagna, MD; R. Caporali, MD, Professor, Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo; L. Abdì-Alì, MD, Department of Rheumatology, IRCCS Foundation S. Maugeri; R. Dore, MD, Radiology Institute, IRCCS Foundation Policlinico S. Matteo; F. Meloni, MD, Department of Hematological, Pneumological and Cardiovascular Sciences, Section of Pneumology, University and IRCCS Foundation Policlinico S. Matteo; C. Montecucco, MD, Professor, Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo.

Address correspondence to Dr. L. Cavagna, Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo, viale Golgi 19, 27100 Pavia (PV), Italy. E-mail: lorenzo.cavagna@unipv.it

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The treatment is still a matter of debate. Although (as for PM/DM-related ILD[8]) corticosteroids have been considered the mainstay treatment[9], their effectiveness in monotherapy is generally limited and unsatisfactory. Immunosuppressants are frequently prescribed because of refractory/relapsing ILD[10,11,12], as recently observed by Stanciu, *et al*[13] in one of the largest cohorts of anti-Jo1 patients yet described. To date, therapies such as cyclophosphamide[14,15] and azathioprine[14,16] have yielded contrasting results. Other immunosuppressants have been used in single case reports or small pilot studies. Good results were obtained with leflunomide[17], mycophenolate[18], rituximab[19,20,21,22,23], anakinra[24], and in particular, tacrolimus[14,25], which acts as a calcineurin inhibitor and principally affects T lymphocytes. Cyclosporine (CYC) is another calcineurin inhibitor found to be effective in PM/DM-related ILD[26] and also in limited series/case reports of antisynthetase syndrome patients with ILD[27,28,29,30]. We describe our observations regarding the longterm effectiveness and safety of CYC for treatment of patients with anti-Jo1 antisynthetase syndrome with corticosteroid-refractory/relapsing ILD.

MATERIALS AND METHODS

Patients. All patients referred to our division between June 1991 and February 2010 with a diagnosis of anti-Jo1-positive antisynthetase syndrome were retrospectively reevaluated for ILD occurrence. Only the patients with corticosteroid-refractory or relapsing ILD were included in our study. In all cases, clinical features and complete investigation results (biochemical and instrumental) were available from disease onset.

Autoantibody profiling. Anti-Jo1 positivity was reassessed for confirmation on frozen and stored serum from all patients and additional anti-extractable nuclear antigen specificities were also tested for on the same samples by EliA fluoroenzyme-immunoassay (Phadia 250 automatic instrumentation, Phadia GmbH).

Pulmonary function tests (PFT). A Vmax 22 system and an Autobox V6200 (SensorMedics) were used to measure lung function. For spirometry, mouth flow was measured using a mass flow sensor and volume was obtained by numerical integration of the flow signal. After at least 4 stable tidal breaths, patients were asked to exhale slowly to residual volume and to then inhale forcefully to total lung capacity. This maneuver was immediately followed by a forced expiration to residual volume. The forced inspiratory flow at 50% of FVC and forced expiratory flows at 50% and 25% of FVC were measured on flow-volume curves. Forced expiratory maneuvers were repeated until reproducible values of forced expiratory volume in 1 s (FEV1) and FVC were obtained[31].

Lung volumes were measured with patients sitting in a body plethysmograph and panting against a closed shutter at a frequency of 1 Hz with their cheeks supported. Predicted values for spirometry and lung volumes were provided by Quanjer, *et al*[32]. The single-breath technique, according to a modified Krogh procedure, was used to determine DLCO[33].

High-resolution computed tomography (HRCT) of the chest. HRCT was performed using the conventional sequential technique from 1991 to 2003, using the 16-detector spiral technique from 2003 to 2008 and the 16- or 64-detector technique from 2008 to 2011. With the sequential technique, about 10 slices were obtained in each examination, with 1 mm thickened, 10 mm interscan space, and about 1–2 mSv radiation dose. With the spiral technique, a volumetric acquisition was obtained and axial and coronal images were reformatted with 1–1.2 mm thickened. Automatic modulation of photon energy and radiation doses depended on patient size and anatomical region. The usual energy and radiation dose was used for baseline CT examination (about 3–4 mSv), while low energy (80–100 Kv instead of 120 Kv) was used in followup studies (about 2–3 mSv). Anti-X screening was used on the skin of all patients studied from 2010, to protect breasts, thyroid, and crystalline lenses.

Clinical and instrumental assessment. We defined the presentation of ILD as acute/subacute when dyspnea began acutely and progressed rapidly (within 4–6 weeks of symptom onset), chronic when dyspnea began insidiously and progressed slowly, and asymptomatic when lung involvement was only instrumental and there were no clinical correlates. Instrumentally, lung involvement was defined by a restrictive PFT pattern (FVC ≤ 80%, FEV1/FVC ≥ 70%, decreased or normal FEV1, and/or < 20% reduction in DLCO) and/or by signs of alveolitis/fibrosis on HRCT. We routinely performed PFT every 2 months in all cases until well established disease improvement/stabilization was reported, then every 6 months thereafter. Chest HRCT was carried out at onset and then every 12 months thereafter or in the case of ILD worsening. A well established and commonly used score, the Kazerooni score[13,34,35], was used to evaluate the extent of ILD at baseline and during followup. This entails scoring each lobe of the lung on a scale of 0–5 for both alveolar (e.g., ground-glass alterations) and interstitial abnormality (e.g., fibrotic lesions such as honeycombing and septal lines) depending on the percentage of each lobe involved and the type of finding observed. The pattern of interstitial involvement was evaluated by HRCT according to American Thoracic Society/European Respiratory Society classification criteria[36]. Kazerooni score and ILD pattern were assessed by our reference radiologist (RD). ILD was considered refractory (or relapsing) in cases of worsening dyspnea, more than 10% FVC or DLCO deterioration compared to either previous or basal tests, and/or when Kazerooni score progressed, even when FVC and DLCO were stable.

Treatment. Initially, all patients were treated with prednisone orally 1 mg/kg/day for at least 1 month; prednisone dosage was then progressively tapered according to clinical/instrumental effectiveness, as previously described. Patients with worsening or relapsing ILD were given CYC (3 mg/kg/day) as additional treatment without increasing the prednisone, which remained unchanged until ILD was under control. In all cases, a clinical and biochemical evaluation was performed every 2 months; CYC dosage was reduced in cases reporting a creatinine increase > 30% compared to baseline values or in the case of uncontrolled arterial hypertension.

Statistical analysis. Data were expressed as median and interquartile range (IQR). FVC, DLCO, Kazerooni score, and prednisone dosages at baseline, after 1 year, and at the last available followup with CYC were compared and analyzed by the paired-samples t-test. Stata 10.1 (Stata Corp.) was used for computation. A 2-sided p-value < 0.050 was considered statistically significant.

RESULTS

From June 1991 to February 2010 we observed 18 patients with anti-Jo1-positive antisynthetase syndrome. Of those patients, 17 showed evidence of ILD according to the selection criteria. All these patients were retrospectively reassessed; ILD onset was acute in 7 cases and chronic in 10 and no patients had asymptomatic ILD. Each of these 17 patients had failed to respond to prednisone within 12 months prior to starting CYC. The median age at ILD onset was 57 years (IQR 49–69). Patients' demographic data and main clinical features are reported in Table 1. HRCT pattern of ILD was consistent with nonspecific interstitial pneumonia in 14 patients and with usual interstitial pneumonia (UIP) in 3; we observed a discrete entity of ground-glass opacities besides honeycombing and reticulation in patients with UIP.

Table 1. Baseline characteristics and progression of patients.

Case	Sex, Age at ILD onset	Serology	Disease Duration Before CYC, mo	Other Typical Antisynthetase -related Features	ILD Pattern (HRCT)	ILD Onset	CYC, mo	CYC Side Effects	CYC Dose start/last, mg/kg/day	PDN Dose at CYC, start/last, mg/kg/day	O_2 Therapy, l/min, at CYC, start/last	Global Outcome
1	M 74	Jo-1/Ro	6	A,M,RP	NSIP	Chronic	57	Creatinine increase	3/0.5	12.5/5	4/0	Dead (car crash)*
2	M 49	Jo-1/Ro	12	A,RP,MH	NSIP	Acute	80	Creatinine increase	3/0.5	10/5	4/1	Lost to followup (associated PAH under CYC)
3	F 57	Jo-1	12	A,M	UIP	Chronic	72	Creatinine increase	3/1.5	10/2.5	—	Lost to followup
4	F 69	Jo-1	6	A,M	NSIP	Acute	96	Hypertension	3	25/2.5	—	Alive
5	F 72	Jo-1/Ro	2	A,M,RP,MH	NSIP	Acute	108	Creatinine increase Hypertension	3/1.5	50/5	4/1	Alive (associated PAH under CYC)
6	M 69	Jo-1	12	A	NSIP	Chronic	120	Creatinine increase	3/0.5	12.5/2.5	—	Alive* (A under CYC)
7	F 71	Jo-1	2	A,M	NSIP	Chronic	38	None	3	50/2.5	—	Alive
8	F 68	Jo-1	2	A,M,MH	NSIP	Chronic	144	Hypertension	3	62.5/2.5	—	Alive
9	M 45	Jo-1	2	A,M	NSIP	Chronic	41	None	3	37.5/—	—	Alive
10	F 40	Jo-1/Ro	6	A,M,RP,MH	UIP	Chronic	228	None	3	17.5/2.5	—	Alive
11	F 45	Jo-1	12	A,M,MH	NSIP	Acute	96	None	3/0	12.5/2.5	—	Dead (respiratory failure)†
12	F 72	Jo-1/Ro	12	A, M	NSIP	Chronic	65	None	3	17.5/5	—	Alive (M under CYC)
13	F 51	Jo-1	6	A,M,RP	NSIP	Chronic	108	None	3	25/5	—	Alive
14	F 51	Jo-1/Ro	2	A,M,RP,MH	NSIP	Acute	192	Creatinine increase Hypertension	3/0.5	50/5	4/0	Alive
15	F 58	Jo-1/Ro	2	A	NSIP	Acute	24	None	3	50/2.5	—	Alive
16	F 49	Jo-1/Ro	2	A,M,RP,MH	UIP	Acute	252	Hypertension	3	37.5/2.5	—	Alive
17	F 50	Jo-1	2	A,M,RP	NSIP	Chronic	30	None	3	37.5/—	—	Alive

* Temporary ILD relapse after short-term CYC withdrawal. † ILD progression after CYC withdrawal. ILD: interstitial lung disease; CYC: cyclosporine; A: arthritis; M: myositis; RP: Raynaud's phenomenon; PAH: pulmonary arterial hypertension; MH: mechanic's hands; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia.

CYC was started 2 months after initiation of corticosteroid therapy in 8 patients (corticosteroid-refractory ILD). In all cases, baseline values of FVC or DLCO worsened and clinical respiratory status deteriorated. However, Kazerooni score was stable in 5 patients and progressed in 3. The remaining patients improved soon after starting prednisone but worsened subsequently (in PFT and clinically). Four patients started CYC 6 months after starting corticosteroid therapy and 5 patients 12 months after starting corticosteroid therapy (relapsing ILD). The Kazerooni score of those patients progressed in 3 and 4 cases, respectively, and was stable in the remaining patients (data not shown).

When CYC was started, all patients had dyspnea and 4 needed O_2 treatment at rest. Other antisynthetase syndrome manifestations were usually effectively controlled by corticosteroids. FVC was reduced in 13 patients (median 60% of predicted value, IQR 56–70), while all patients had DLCO reduction (median 60% of predicted value, IQR 50–62.75). The median Kazerooni score was 16 (IQR 7–18). When CYC was started, median prednisone dosage was 25 mg/day (IQR 12.5–50).

After initiation of CYC, O_2 therapy was discontinued within 2 months in 2 patients (Patients 1 and 14) but continued in 2 cases, although it was reduced from 4 l/min to 1 l/min (Patients 2 and 5). During the first year of the study, all patients were responsive to CYC and their respiratory symptoms improved. During the first year of followup, other systemic disease manifestations were effectively controlled. At 1 year of treatment, a significant improvement was reported in FVC (median 75% of theoretical value, IQR 67–85; $p = 0.0006$), DLCO (median 66% of theoretical value, IQR 57.25–72.25; $p = 0.0010$), and total Kazerooni score (median 10, IQR 4–15; $p = 0.0002$) because of reduction of ground-glass opacity. In 2 patients with HRCT pattern of UIP, the reduction of ground-glass opacities, while evident, was not sufficient to reduce the Kazerooni score. Prednisone was therefore tapered to a median value of 2.5 mg/day (IQR 2.5–5; $p < 0.0001$).

In the subsequent years, 5 patients (Patients 4, 5, 8, 14,

16) started low-dose calcium channel blocker treatment because of arterial hypertension, 3 patients reduced CYC (Patients 2, 3, 5), and 3 ceased CYC (Patients 1, 6, 14) because of a rise in creatinine; Patient 11 withdrew from CYC treatment voluntarily and without giving reasons. ILD relapsed in 3 out of 4 patients who stopped CYC (Patients 1, 11, 14); restarting low-dose CYC (0.5 mg/kg/day) in Patients 1 and 14 together with an increase in prednisone dosage (25 mg/day with subsequent tapering) led to ILD control, with no subsequent problems. Patient 11, who spontaneously stopped CYC after 96 months, was lost to followup until a subsequent emergency admission to our division 10 months later with severe acute respiratory failure, which was fatal. There was 1 other death after 57 months of followup, but it was not attributed to antisynthetase syndrome (auto accident). Two patients (Patients 2 and 3) were lost to followup after 80 and 72 months, respectively. At the last eligible followup (median 96 mo, IQR 57–120), FVC (median 81% of theoretical value, IQR 69–89; p = 0.0274) and Kazerooni score (median 9, IQR 4–14; p = 0.0226) had statistically improved, whereas DLCO (median 69% of theoretical value, IQR 55.25–74.5; p = 0.2809) and prednisone (median 2.5 mg/day, IQR 2.5–5; p = 0.1635) were substantially stable compared to 1-year results.

Regarding other disease manifestations, during the longterm followup we observed the appearance of myositis in 1 case (Patient 6, after 21 mo receiving CYC) and arthritis in another (Patient 12, after 24 mo receiving CYC)[37]. Prednisone was then increased to 25 mg/day in Patient 6 with subsequent tapering, whereas methotrexate (15 mg every week) was added in the case of Patient 12. Treatment was effective in all cases. As described[38], we diagnosed pulmonary arterial hypertension in 2 cases (Patients 2 and 5) after 84 and 72 months, respectively, of CYC treatment. The overall characteristics of patients enrolled are given in Table 1. FVC and DLCO fluctuations during the entire period of study are shown in Figure 1. Table 2 reports the mean, SD, median, and IQR of FVC and DLCO in the first 2 years of CYC. Kazerooni score fluctuations during followup are given in Figure 2. The specific findings are shown in Figure 3, which describes PFT changes during followup in patients with UIP.

DISCUSSION

Although ILD is a well known manifestation of antisynthetase syndrome, the optimal therapeutic approach in this setting is still debated. Similarly to PM/DM-related ILD, first-line treatment is generally based on corticosteroids[8], although second-line drugs are frequently needed because of the high percentage of treatment failure[10,11,13,39]. Further, the need for immunosuppressants is particularly relevant in anti-Jo1 antisynthetase syndrome with ILD, as confirmed by Stanciu, *et al*[13]. Our results substantially confirm the ineffectiveness of corticosteroids alone in this setting, reporting 100% of ILD unresponsiveness or relapse within 12 months of appearance of lung involvement. Regarding second-line drugs, several immunosuppressants have been tried, but only case reports and small pilot studies (without placebo-controlled trials) are available because of the disease's rarity. Good results have been described with anakinra[24], mycophenolate[18], and leflunomide[17] in single-case reports. Cyclophosphamide and azathioprine have yielded conflicting results; studies have reported both the effectiveness[15] and ineffectiveness[14,16] of treatments. Moreover, the good results obtained with tacrolimus[25] and rituximab[19,20,21] in single-case descriptions have also been confirmed by small pilot studies[14,22,23].

Our choice of CYC in 1991 was driven by the description of a patient with steroid-resistant ILD associated with PM successfully treated with CYC[26]. The first cases reporting effectiveness of CYC in antisynthetase syndrome with steroid-refractory ILD were published in the late 1990s[27,28,29,30], although negative outcomes have also been reported[40]. To date, these studies involved few patients, the largest series involving 4[29], 5[30], and 7 cases[40]. Reports on tacrolimus[14] and rituximab[22,23] also involved fewer patients than our case series. The maximum length of followup previously reported in similar studies is 36 months in median[14]. Hence, to our knowledge, ours is the largest and longest study published on the effectiveness of a single immunosuppressant on ILD in antisynthetase syndrome. Moreover, we evaluated only 1 antisynthetase specificity. This may be seen as a strong point of our study because different antisynthetase specificities are associated with different disease profiles[7,41,42]. Regarding patients' clinical features, our results are in agreement with those of Hervier, *et al*[7]. In fact, anti-Jo1 patients exhibited a wide range of manifestations other than ILD, such as myositis and arthralgias/arthritis. Our data therefore confirm the effectiveness of CYC in this setting. CYC improved not only the clinical respiratory status of all patients and for a long period of time, but also their FVC and DLCO. Further, in comparison to previous studies, our results were reinforced by the reduction of ground-glass opacities, assessed by Kazerooni score[34]. It is interesting that in the 2 patients with a stable Kazerooni score, we also observed a reduction in ground-glass opacities. The improvement, however, was not significant enough to reduce the score used. These 2 patients had HRCT findings of UIP, characterized by the occurrence of honeycombing and reticulation and, to a lesser extent, by ground-glass opacities. Therefore, in our population, the HRCT pattern described did not influence the evolution of ILD, because patients presenting with UIP were also responsive. However, similar to data given in the literature, the HRCT pattern we found was mainly nonspecific interstitial pneumonia[11].

It is also interesting that improvement was observed

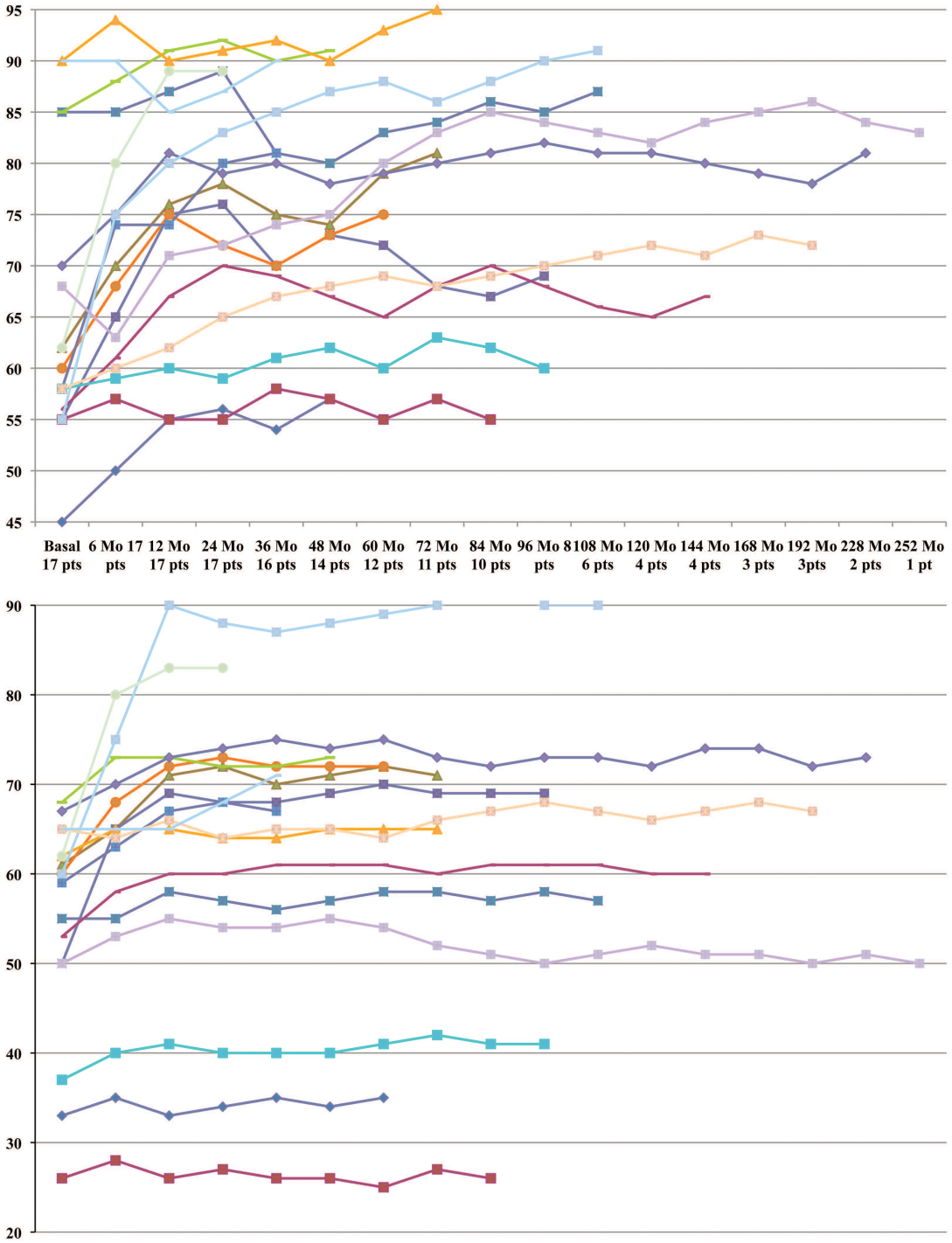

Figure 1. Forced vital capacity (top) and DLCO (bottom) fluctuations during cyclosporine treatment (shown as percentage of theoretical value).

when ILD onset was acute and when anti-Ro antibodies, frequently found with anti-Jo1[43,44], were detected. Indeed, acute onset[45,46] and anti-Ro occurrence[13,47] have been described as negative prognostic factors for ILD progression in antisynthetase syndrome. Moreover, our data showed that patients' improvement was particularly evident in the first months of therapy with CYC. This could be related to the fast drop in ground-glass opacities soon after starting CYC. The lack of intermediate HRCT controls, however, does not allow us to confirm this hypothesis. It is interesting that both FVC and Kazerooni score were slightly better at the last eligible followup than at 1 year. This indicates the longterm

Table 2. Mean, median, and interquartile range (IQR) of forced vital capacity (FVC) and DLCO during the first 2 years of cyclosporine (CYC) treatment.

	Basal		6 Mo. CYC		12 Mo. CYC		24 Mo. CYC	
	FVC	DLCO	FVC	DLCO	FVC	DLCO	FVC	DLCO
Mean	65	55	71	60	75	63	76	63
SD	14	12	13	14	12	16	12	16
Median	60	60	70	65	75	66	78	68
IQR	56–70	50–62.75	61–80	55–68	67–85	57.25–72.25	70–87	57–72
No. patients	17		17		17		17	

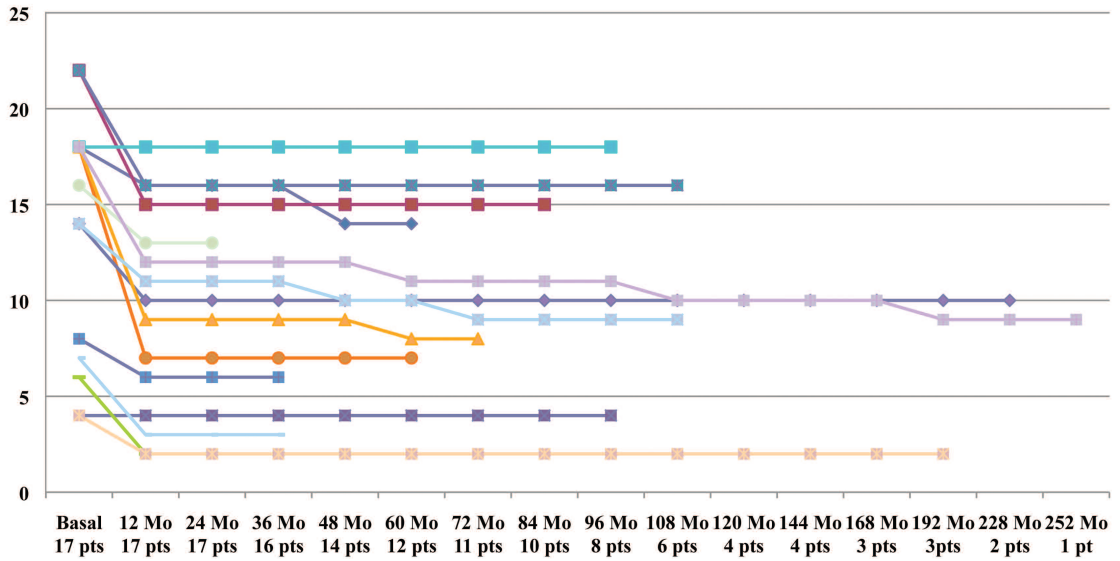

Figure 2. Kazerooni score fluctuations during cyclosporine treatment.

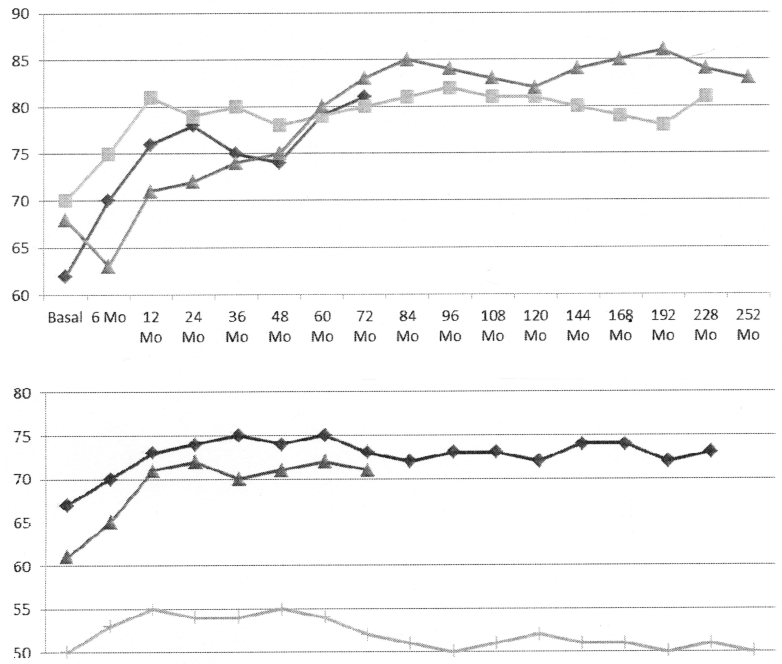

Figure 3. Forced vital capacity (top) and DLCO (bottom) fluctuations in patients with usual interstitial pneumonia during followup (expressed as percentage of theoretical value).

action of CYC on ILD mechanisms. Further, we have shown that CYC was also effective at low doses (suggested by the lack of ILD flares in patients who tapered CYC because of the drug's side effects). It is also interesting to observe that ILD relapsed in all but 1 of the patients who withdrew from CYC. In these patients, low-dose re-treatment with CYC induced control of lung disease. The patient who refused CYC re-treatment died because of ILD progression. Our data suggest that CYC dosage in this setting can be tapered to reduce side effects, while still limiting the risk of ILD relapse. However, there is 1 study that did not confirm the effectiveness of CYC in this setting[40], but the lack of PFT and an established HRCT score for ILD does not allow full interpretation of the results.

Considering data in the literature, both B and T cells seem to be good targets for ILD treatment in antisynthetase syndrome. Good results have been had with rituximab[22,23], tacrolimus[14,25], and CYC[27,28,29,30] in the majority of cases described. The larger number of patients and the longer followup on tacrolimus and CYC could support the early use of these drugs in this setting (Table 3). Indeed, the rationale for targeting T cells in antisynthetase syndrome is based on several possible mechanisms. Data in the literature indicate that autoreactive Jo1-specific T cells play a primary role in the appearance of different manifestations (ILD in particular) in a murine model of antisynthetase syndrome[48]. Moreover, CYC could also inhibit nuclear factor-κB (NF-κB)[49,50,51], a transcription factor family that transmits signals from the cell surface to the nucleus, resulting in transcriptional effects on the genes involved in inflammation, cell differentiation, and survival[52]. NF-κB complex has been associated with the appearance of idiopathic inflammatory myopathies in general and with DM in particular[53], which is similar to antisynthetase syndrome. Further, the inhibition of NF-κB in an experimental murine model of chronic lung fibrosis led to reduction of collagen deposition and lung injury in both acute and chronic phases[54].

Studies have reported CYC involvement in the down-regulation of tumor necrosis factor-α and the upregulation of interleukin 10 in several conditions[55,56,57,58]. Taking into account the genetically determined imbalance of serum levels of tumor necrosis factor-α and interleukin 10 in anti-Jo1 patients[59], these mechanisms could also explain the efficacy of CYC in this setting.

We are aware of the limitations of this work. The main criticism is that it is a single-center study and is therefore open to the risk of selection bias. Our study is neither prospective nor placebo-controlled and is limited by the small number of patients evaluated.

Despite the limitations, our results suggest that CYC is useful for both induction and longterm maintenance of remission in antisynthetase syndrome patients with corticosteroid-refractory ILD. It is conceivable that adding CYC to corticosteroids shortly after onset of ILD may be effective in disease control. Further comparative studies involving a larger cohort of patients are needed to confirm our results.

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Table 3. Main studies/case reports evaluating effectiveness of calcineurin inhibitors (cyclosporine and tacrolimus) in antisynthetase patients with ILD.

Study	Pts Assessed	No. Anti-Jo-1 Pts	Immunosuppressant	Followup on Immunosuppressants, mo	Patients Improved	ILD Improvement PFT	ILD Improvement HRCT
Present study	17	17	Cyclosporine	96**	17/17	FVC, DLCO	Kazerooni score
Sauty[29]	4	4	Cyclosporine (+ azathioprine)	18**	4/4	TLC, FVC, DLCO	NA
Tellus[27]	1	1	Cyclosporine	60	1/1	FVC, DLCO	NA
Wilkes[14]	12	12	Tacrolimus	36**	12/12	FVC, DLCO	NA
Guglielmi[25]	1	1	Tacrolimus	6	1/1	NA	NA
Koreeda[30]	5*	5	Cyclosporine	14**	4/5	Yes†	Yes†
Ingegnoli[40]	7††	7	Cyclosporine	12	0/7	NA	Progression†

* Other 9 patients not taking cyclosporine. ** Median. † Data not further specified. †† Eight other patients taking cyclophosphamide. ILD: interstitial lung disease; PFT: pulmonary function tests; HRCT: high-resolution computed tomography; FVC: forced vital capacity; TLC: total lung capacity; NA: not available.

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